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Initiation and Execution of Locomotion Elicited by Diencephalic Stimulation: Regional Differences in Response to Nembutal[1]

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SKLOW, B. AND H. M. SINNAMON. *Initiation and execution of locomotion elicited by diencephalic stimulation: Regional differences in response to Nembutal.* PHARMACOL BIOCHEM BEHAV 36(4) 719–724, 1990.—At moderate levels of Nembutal, within the anesthetic range, locomotor stepping can be elicited by brain stimulation. We determined if Nembutal (7, 14 and 28 mg/kg) had different effects on locomotion elicited by stimulation at different brain regions. Two regions were compared: the medial forebrain bundle (MFB, 13 sites) and the areas medial and dorsal to it (MED/DORSAL, 20 sites). Locomotion was produced by electrical stimulation (50 μA, 0.5 msec pulses, 10 to 160 Hz) of unrestrained rats in a rotary runway. The latency to initiate locomotion and the time to complete 1 revolution of the rotary were measured. With no drug, MFB locomotion was initiated sooner but took longer to complete than MED/DORSAL locomotion. Nembutal at 7 mg/kg did not affect initiation of MFB or MED/DORSAL locomotion. Nembutal at 14 mg/kg shortened MFB initiations, but this dose prolonged MED/DORSAL initiations. Initiations with both types of sites were blocked with 28 mg/kg. The 7 and 14 mg/kg doses prolonged the locomotor completion times of the MFB sites but not of the MED/DORSAL sites. The results indicate that the response to Nembutal differs qualitatively for locomotion elicited by stimulation of the MFB and locomotion elicited by stimulation of the medial and dorsal hypothalamus. The mechanisms underlying the difference remain to be elucidated; they may relate to nonlocomotor behaviors also elicited by stimulation or to the motivational states reflected in those behaviors.

Locomotion Nembutal Electrical stimulation Rats

THE compatibility of anesthesia with the capacity to initiate locomotor stepping has been known since Brown in 1913 (3) showed that cats, guinea pigs and rabbits administered chloroform or ether showed periods of spontaneous rhythmic hindlimb flexions that resembled the locomotor patterns characteristic for a given species. More recently, Viala and Buser (36) have provided a detailed description of the fictive version of this phenomenon as expressed in the motor nerves of the paralyzed rabbit anesthetized with Nembutal. Waller in 1940 (37) and Grossman in 1958 (12) used anesthetized cats to identify diencephalic and midbrain sites at which electrical stimulation could elicit stepping movements. Sirota and Shik (34) elicited treadmill stepping by Nembutal-anesthetized cats by stimulation of the posterodorsal midbrain. Apparently the first studies of locomotor stepping in the anesthetized rat were by Mel'nikova (18,19) who stimulated the medial diencephalon or posterodorsal midbrain to elicit stepping on a treadmill.

Using the anesthetized rat held in a stereotaxic apparatus and suspended over a treadmill belt or a wheel, the diencephalic and brainstem locomotor regions have been mapped by electrical stimulation (26, 29, 32). In the diencephalon, locomotor sites in the anesthetized rat correspond generally to those demonstrated in the awake rat (22). The effective areas include both the medial and lateral hypothalamus and the general region of the zona incerta. On the basis of anatomical differences alone, one could expect that the characteristics of the locomotion elicited by stimulation of these regions might differ. In studies which requred that locomotion be repeatedly elicited over several hours (11, 15, 31–33), we have noted that sites in the lateral hypothalamus are particularly reliable in supporting vigorous locomotion. Sites in other regions of the diencephalon also could support vigorous locomotion but the locomotor initiation in these cases appeared to be more sensitive to depression by the hourly injections of 7 mg/kg Nembutal used to maintain the anesthetized state.

This study used awake rats with chronic stimulation electrodes to compare the sensitivity to Nembutal of sites within and contributing to the medial forebrain bundle (MFB group) to sites outside of this system in the zona incerta and medial hypothalamus

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ABBREVIATIONS

AH	Anterior hypothalamic nucleus
BSTPO	Preoptic bed nucleus of stria terminalis
DA	Dorsal area of the hypothalamus
DM	Dorsomedial nucleus of the hypothalamus
LH	Lateral hypothalamus
LPO	Lateral preoptic area
MM	Medial mammillary nucleus
MPO	Medial preoptic nucleus
PH	Posterior hypothalamic nucleus
PMD	Dorsal premammillary nucleus
SO	Supraoptic nucleus
ST	Subthalamic nucleus
VM	Ventromedial nucleus of the thalamus
VMH	Ventromedial nucleus of the hypothalamus
ZI	Zona incerta

(MED/DORSAL group). Regional differences would have both theoretical and methodological implications. First, regional differences could suggest the existence of functional and neurochemical differences in the pathways involved in locomotion. Second, differences would indicate an important limitation in the use of the anesthetized rat for locomotor studies if certain locomotor sites proved to be more depressed by the drug.

METHOD

Subjects and Surgery

Male Sprague-Dawley rats (N = 18) weighing between 268 and 472 g were used. They were housed on a reversed light cycle in group or individual cages. Chronic stimulation electrodes were implanted stereotaxically in animals anesthetized with intraperitoneal injections of either Chloropent (3.2 ml/kg) or Nembutal (45 mg/kg). Supplemental anesthesia was provided by an injection of 0.5 ml of 2% lidocaine into the scalp incision and by intraperitoneal injections of 7 mg/kg Nembutal as needed. Three stimulation electrodes were aimed for various sites in the diencephalon. The electrodes were Teflon-insulated stainless steel wires 125 μm in diameter that were cut to expose the cross section of the tip. An uninsulated wire was wrapped around four screws placed in the skull and served as the anodal return line for the stimulation circuit. Amphenol pins attached to the electrodes and return wire were inserted into a plastic strip which was secured to the skull by dental cement. Topical antibiotics were applied.

Measurement of Locomotor Initiation and Execution

The rotary runway was made of Plexiglas with an outer diameter of 30 cm and a path width of 8.3 cm. The path length was 45 cm inside and 96 cm outside. Three infrared sensors were spaced equidistantly around the circumference of the runway. A custom circuit rejected sensor signals occurring consecutively at the same sensor that were due to head movements and rearing. Occasional spurious sensor signals not due to locomotion were visually identified and deleted. The elapsed time from the start of stimulation to the rat's movement to the first sensor was recorded with a resolution of 1.0 sec. The amount of movement required to activate the sensor was a maximum of 30 cm but averaged approximately 15 cm. Stimulation continued until the rat passed two additional sensors (approximately 60 cm of additional travel). The rotary was enclosed in a ventilated, sound-attenuated box equipped with a one-way window and illuminated with a 7-W centrally located light.

Qualitative visual observations of the rat's behavior during stimulation were recorded. For ataxia the following categories were used: 1) normal locomotion, 2) moderate uncoordination present (wide stance, some wobble in gait), 3) marked uncoordination (extreme wobbling gait, staggering), 4) loss of upright posture of the limbs and head (crawling), 5) immobility. Additional observations were made of nonlocomotor behavior during stimulation. The major categories were rearing, head movement direction, body turns, investigatory sniffing, grooming, and halting of locomotion. A behavior that occurred on the majority of predrug trials in a session and for at least two of the three sessions was defined as characteristic of a site.

Electrical Stimulation

To facilitate the regional analysis, the area of stimulation was held constant by using a fixed current of 50 μA. Stimulation was delivered through a flexible cable connected to a communtator and consisted of trains of cathodal rectangular pulses of 0.5-msec duration. The current was monitored through a 1-KΩ resistor on an oscilloscope throughout the test. A train with increasing steps of pulse frequencies was used in order to allow the testing of the locomotor frequency-duration threshold of a site on each trial. Specifically, the train consisted of 50 sec of stimulation in which the pulse frequency doubled every 10 sec. The frequency initially was 10 Hz, and it progressively stepped to 20, 40, 80 and ultimately to 160 Hz. Thus, if locomotion was detected at 15 sec, the frequency at that point would have been 20 Hz. Logic control circuitry terminated the stimulation train when the locomotor completion requirement was met, i.e., two additional locomotor signals were produced (approximately 5 sec later). Stimulation terminated automatically if the completion requirement was not met after 10 sec of 160-Hz pulses (50 sec of total stimulation).

Procedure

Preliminary tests to determine which of the three chronic electrode sites would support locomotion followed a minimum of 4 days of recovery from surgery. Sites that showed consistent locomotion to 5-sec trains of 50-Hz pulses were selected for further testing. Of the 18 rats, 4 were tested with one electrode, 13 were tested with two electrodes, and 1 was tested with three electrodes.

A test session followed a 5–10-min adaptation period without stimulation. For the remainder of the session, every 90 sec a trial was presented in which a site was tested with a stimulation train having a maximum duration of 50 sec. The minimum interval between the end of a train and the onset of the next was 40 sec. If the rat had more than one tested site, each would be tested in turn on successive trials. The duration of the predrug phase of the session was 30–40 min. For the Nembutal injection, the rat was removed from the rotary and injected intraperitoneally. Testing continued as before within 5 min. If the drug blocked the initiation of locomotion for all of the sites, the interval between the end of stimulation offset and onset was extended to 100 sec. This pattern continued until locomotion returned with stimulation at one or more sites at which time the 40-sec intertrial interval was reinstated. The session was terminated after at least a 45-min postinjection period had elapsed and when postdrug latencies began to return to predrug levels.

The doses of Nembutal tested (7, 14 and 28 mg/kg) represented the range used in locomotor studies (11, 15, 30–32) of rats held in a stereotaxic apparatus. They were tested in three successive sessions in the rotary. The volumes of all injections were brought to 2 ml/kg by the addition of saline. A minimum interval of 3 days separated the sessions. Occasionally a test session was repeated because of an apparatus failure or a misplaced injection. A total of 6 sites in 5 rats had repeat tests at 28 mg/kg.

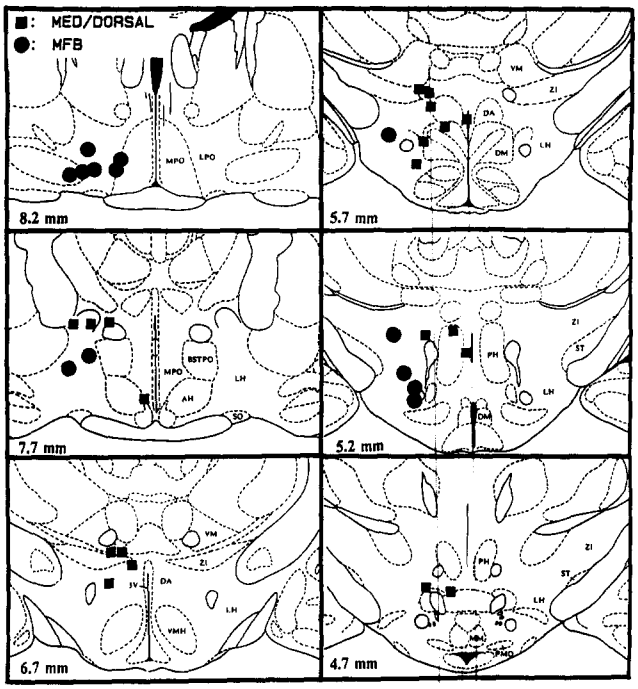

FIG. 1. The locations of 33 stimulation sites schematically illustrated on drawings adapted from the atlas of Paxinos and Watson (23). All sites are arbitrarily illustrated on the left of each panel. Sites in the MFB group are represented by the solid circles; sites in the MED/DORSAL groups are represented by the solid squares. The number at the lower left of each panel refers to the distance from the earbar zero.

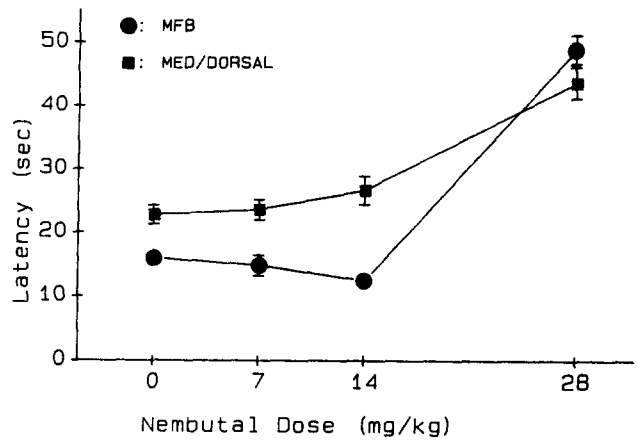

FIG. 2. Effect of Nembutal injected intraperitoneally on mean (±SEM) latency to initiate locomotion in the rotary by electrical stimulation in 13 MFB sites and 20 MED/DORSAL sites. Each dose was tested in a separate session which was divided into 20-min predrug and postdrug periods. For each site the median of the three predrug periods were averaged to provide an average predrug latency. The mean of these values is represented as the latency at 0 mg/kg. The other values are based on the median latencies in the 20-min periods beginning 6 min after the injections. SEM's smaller than the symbol are not represented.

To assess the effects of Nembutal, each electrode site was characterized by summary values for the two locomotor latencies (initiation and completion) for a predrug and a postdrug period for each of the three sessions (7, 14, 28 mg/kg). The predrug values were based on the 20-min periods preceding the drug injection in the three sessions. The median for all of the available trials (typically 7) in the predrug period was derived and the mean of these medians was determined to arrive at the single predrug value for a site. For the postdrug periods, the median value was determined for the trials in the 20-min period beginning at 6 min after the injection. Subsequent trials were found to add no significant information. With the 28 mg/kg injections the typical effect was a complete block of locomotion, so an additional determination, block duration, was made. It was defined as the time from the first trial with blocked locomotion to the fourth consecutive trial with recovered locomotion.

Histology

After the rat was given the lethal dose of Nembutal, it was perfused through the heart with saline followed by 10% Formalin. The brain with electrodes in situ was fixed in Formalin for at least 72 hr. The brain was cut on a cryostat microtome in 48-μm transverse sections. The sections were stained with cresyl violet, viewed under a Bausch and Lomb projector at a magnification of 23. The deepest point of the electrode tracks were projected onto drawings of the brain taken from the atlas of Paxinos and Watson (23).

RESULTS

The locations of the stimulation sites are illustrated in Fig. 1. The 13 sites designated as MFB are indicated by solid circles; they ranged from the lateral preoptic area (LPO) anteriorly to the posterior aspects of the lateral hypothalamus (LH). The 20 sites designated as MED/DORSAL are indicated by solid squares; they were located in the medial aspects of the hypothalamus [the anterior (AH), dorsomedial (DM), and posterior (PH) nuclei] and the anterior zona incerta (ZI). The uncertainties in this type of classification are recognized.

The effects of three doses of Nembutal on the initiation of locomotion in the two groups is illustrated in Fig. 2. First, it should be noted that the predrug initiation latencies differed in the two groups. The MFB group's latencies averaged 15.9 (±1.12, SEM) sec and the MED/DORSAL group's latencies averaged 22.8 (±1.52) sec. This difference was significant, $t(31)=3.24$, $p<0.01$. The initiation latencies of neither group were affected by the lowest dose of Nembutal (7 mg/kg), but qualitative differences between the groups appeared at the 14 mg/kg dose. Relative to their predrug initiation latencies, every site in the MFB group showed a decrease [mean latency = 12.5 (±1.26) sec, $t(12)=6.51$, $p<0.01$]. The 12.5-sec latency indicates that locomotion with the typical MFB site began within 1–2 sec after the pulse frequency stepped from 10 to 20 Hz. The very low variability of the MFB group suggests the operation of a floor effect here. By contrast, relative to their predrug values the initiation latencies of the MED/DORSAL group were prolonged by 14 mg/kg Nembutal [mean = 26.7 (±1.61) sec, $t(18)=2.48$, $p<0.05$]. Two of these sites had some trials in which locomotor initiation was blocked in the 20-min postdrug period and one site had initiation blocked on all trials.

The highest dose of Nembutal (28 mg/kg) virtually abolished locomotion during the 20-min postdrug period and the effect did not seem to differentiate the two groups. All but one of the MFB sites and 14 of the 20 MED/DORSAL sites had initiation completely blocked. The durations of the blocks for the MFB group [mean = 18.4 (±2.6) min] and for the MED/DORSAL group [mean = 29.2 (±5.56) min] did not differ significantly, $t(31)=1.42$, $p>0.10$.

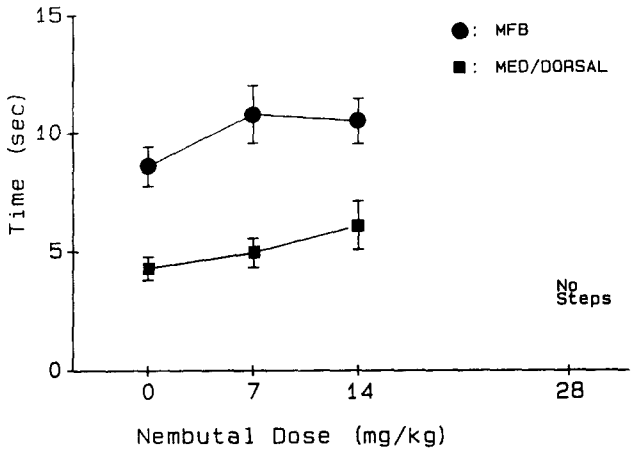

FIG. 3. Effect of Nembutal on locomotor execution defined as the time to complete one revolution around the rotary runway. Same format as Fig. 2.

The effect of Nembutal on the completion of locomotion once initiated is illustrated in Fig. 3. Again the two groups differed in the predrug measures. The MFB group which walked sooner than the MED/DORSAL group took twice as long as that group to complete one revolution in the rotary, $t(31)=4.76$, $p<0.001$. The two groups also showed a quantitative difference in the response of the completion measure to Nembutal. The time to complete stepping by the MFB group was increased by both the 7 and 14 mg/kg doses, $t(12)>2.18$, p's<0.05. However, for the MED/DORSAL group, the increases in the time to complete stepping were less consistent and approached significance only for the 14 mg/kg dose, $t(18)=1.80$, $p<0.10$. In summary, the relatively long completion times of the MFB group were further lengthened by the lower doses of Nembutal, but the relatively short execution times of the MED/DORSAL group showed little or no response.

The increased completion times of the MFB group produced by 14 mg/kg Nembutal were not associated with any consistent ataxia of gait. Only two of the 13 MFB sites showed moderate ataxia on the majority of trials. Moderate to marked ataxic gait was displayed by 7 of the 20 sites in the MED/DORSAL group. Category 4, loss of postural support while maintaining locomotion, was rarely observed; this pattern appeared to mark the transition to complete failure of initiation with the highest dose of 28 mg/kg. In general, the ataxia rating did not correlate with the temporal measures of locomotion at the two lower doses.

The finding that the more rapidly initiating MFB group had longer completion times than the more slowly initiating MED/DORSAL group suggested that the two measures could be inversely related. This unexpected inverse relationship between mean initiation latency and mean completion time in the predrug condition proved to be reliable for the MED/DORSAL group, $r(18)=-.63$, $p<0.01$, and for both groups combined, $r(31)=-.66$, $p<0.01$, but for the MFB group alone which had low variability, the correlation did not reach significance. The overall correlation indicates that the two locomotor measures are not independent. Long initiation times were associated with short completion times.

Nonlocomotor behaviors were highly variable both within trials for a given site and between sites but there were some indications of a differentiation between the two groups of sites. It was common for the MFB group to show locomotion *concurrent* with rearing and upward head movements. Eight of the 13 MFB sites showed this pattern on the majority of predrug trials in at least two of the three sessions. Only one of the 20 MED/DORSAL sites showed this pattern. The difference was significant, $\chi^2(1)=10.15$, $p<0.01$. On the other hand, it was common for the sites in the MED/DORSAL group to show rearing and/or grooming *before* the locomotion was initiated. This pattern was displayed by 9 of the 20 MED/DORSAL sites, but it was also seen in 3 of the 13 MFB sites, and the groups did not differ significantly.

DISCUSSION

This study has two principal findings. First, electrical stimulation of the medial forebrain bundle elicited locomotion that differed from the locomotion elicited by stimulation of the medial hypothalamus and zona incerta. The clearest difference was in the initiation component but there may be independent differences in the execution component and in the integration of locomotion with other behaviors. Second, the initiation of locomotion elicited by stimulation of the two groups of sites responded differently to Nembutal. The long initiation latencies of the medial and dorsal sites were further lengthened by Nembutal and the relatively short initiation latencies of the medial forebrain bundle sites were decreased by Nembutal. To be discussed here are the following points: the mechanisms that might operate to produce the regional differences in the initiation of the elicited locomotion, the mechanisms that might account for the regional differences in the response to Nembutal, the methodological significance of these differences, and finally a motivational perspective on locomotor initiation and execution.

The regional differences in predrug locomotor initiation latencies may relate to regional differences in signal transmission. With the stimulation conditions used here, the MFB locomotion began after approximately 6 sec of 20-Hz stimulation and the MED/DORSAL locomotion began after approximately 2 sec of 40-Hz stimulation. The two groups of sites may integrate the effects of each pulse over time differently such that the summation level required for initiation is reached with fewer pulses with the MFB sites. Greater efficiency could reflect either a greater density of the locomotor fibers, longer duration postsynaptic potentials, greater synaptic security or fewer axonal propagation failures. The determination of the bases for regional differences in the effect of pulse frequency on locomotor initiation appears to be a fruitful direction for future work.

Differential involvement of GABA synapses in the two groups of locomotor sites may contribute to the regional differences in sensitivity to Nembutal. Barbiturates enhance GABA-based presynaptic and postsynaptic inhibitory transmission (13) and one site of action is the GABA-A receptor complex which functions as a chloride iontophore and incorporates recognition sites for benzodiazepines and picrotoxin (7). Nembutal and picrotoxin act oppositely on the conductance channels (35). At low concentrations, Nembutal potentiates the activation of chloride channels by GABA (17,21) and at higher concentrations it appears to directly produce the same effect (2).

Depression of locomotion by Nembutal could be due to the potentiation of tonically active, inhibitory GABA circuits. Injection of the GABA antagonist picrotoxin into the preoptic basal forebrain elicits locomotion in the anesthetized rat (29). In the posterior dorsal midbrain of the cat and rat, picrotoxin produces locomotor stepping (9) and GABA agonists block stepping (4, 9, 24). In the anterior ventral tegmental area of the rat, GABA agonists produce hypoactivity (1) and GABA antagonists elicit locomotion (1,20). Injection of a GABA antagonist into medial nuclei of the hypothalamus elicits locomotion with a jumping component, an association which suggests a functional link to the defensive system of the dorsal midbrain (6). Locomotion elicited by injections in the lateral hypothalamus is not associated with jumping (6). These latter findings suggest that both medial and

lateral hypothalamic locomotor systems are under tonic inhibitory control by GABA circuits. Further, they suggest that the links of the medial system to an aversive system could impart a particular sensitivity to a general anesthetic.

Nembutal potentiation of GABA transmission also could operate in a disinhibitory role in the cases in which the 14 mg/kg dose facilitated locomotor initiation for the MFB sites. In the ventromedial midbrain caudal to the level of the anterior interpeduncular nucleus, GABA agonists increase locomotor activity (1,27). In the cat, injections of a GABA agonist into the posterior hypothalamus produce behavioral activation (16). Injection of a GABA agonist into the dorsal raphe, located in the ventral central gray, also increases locomotion (25,27). Finally, in the nucleus accumbens, GABA injections at low doses increased locomotion in the rat (14). In summary, Nembutal's actions as a GABA agonist may provide a clue to its differential effects on locomotor systems but other possible mechanisms should not be dismissed.

The regional differences in the initiation of elicited locomotion point to a potentially important limitation in the use of the anesthetized rat in studies of locomotion. Locomotion elicited by stimulation in dorsomedial hypothalamic and zona incerta sites is more sensitive to depression by Nembutal than locomotion produced by stimulation in lateral hypothalamic sites. Thus, a bias toward false negatives would be expected in mapping studies under anesthesia (26, 30, 32) in which a site is tested only briefly. Caution is therefore warranted in the interpretation of negative sites in any map based on the anesthetized rat. To minimize the bias, the anesthetic level must be controlled to maintain the anesthetic and sedative effects while minimizing the locomotor depressant effects.

Differences between the MFB and MED/DORSAL groups were also found in the locomotor execution measure and its response to Nembutal. The execution measure was inversely related to the initiation measure, and this dependence presents raises problems for interpretation. The stimulation intensity was higher in cases when the rat was slower to initiate locomotion. For example, in the predrug condition, the average MED/DORSAL site had an initiation latency of 22.8 sec, and therefore the execution phase began under a pulse frequency of 40 Hz. The average MFB site had an initiation latency of 15.9 sec and therefore the execution phase began under 20 Hz. Thus, the possibility is raised that the difference between two groups in the time to complete the stepping requirement was secondary to the difference in initiation studies before the differential effect of Nembutal on the execution of locomotion elicited by stimulation of the two groups of sites can be accepted.

Nonlocomotor behaviors and their interaction with initiation and execution measures indicate that motivational factors will need to be controlled in future studies. With many MED/DORSAL sites, rearing frequently preceded the locomotor response which was rapid. This pattern appears to be similar to the darting pattern described by others with activation of medial sites (6) and associated with a defensive state (6, 8, 28) characterized by behavioral suppression, orienting toward escape routes and finally escape locomotion. With many MFB sites, in accord with previous studies (5,6), locomotion frequently appeared first and then was mixed with rearing and upward head movements. Stimulation in the MFB sites associated with reward (10) could produce locomotion which normally leads to appetitive stimuli located through investigatory head movements. The locomotion would be associated with head movements and have a less driven, more discontinuous quality. These considerations point to the complexities that underlie the study of locomotor initiation in the awake animal. These complexities are as confounding as those of the anesthetized rat, and it is suggested that an effective stategy will use a variety of approaches.

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